REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested.

The Office Action Summary correctly indicates that claims 9, 10 and 12 were pending in the application.

Claims 13-16 have been added. Claims 13 and 14 specifically recite Alzheimer's disease and claims 15 and 16 specifically recite Parkinson's disease, which are conditions included among the group of conditions recited in claim 12. No prohibited new matter has been introduced by way of the above amendments.

Withdrawn Rejection And Consequent Patentability of Claims 13 and 14

In the Office Action mailed April 10, 2007, the Examiner has withdrawn the rejection of claims 9, 10 and 12 under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent Number 5,523,322 (Blache) in view of Nevia et al. (Brazilian Journal of Medical and Biological Research, 30:599-604, 1997), because Applicant has demonstrated that no link between platelet aggregation and Alzheimer's disease was known at the time of the invention. Therefore, there would have been no reason for a person of ordinary skill in the art to consider the platelet aggregation effects taught by Blache in choosing a treatment for Alzheimer disease.

Claims 13 and 14 have been added specifically reciting treating Alzheimer's disease. In view of the withdrawal of the rejection, Applicants respectfully request an indication that claims 13 and 14 are allowable.

Rejections maintained under 35 U.S.C. § 103

Blache and Lechner

Claims 9, 10 and 12 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent Number 5,523,322 ("Blache") in view of Lechner et al., *Wiener Medizinische Wochenschrift*, 136:387-91, 1986 ("Lechner"). The rejection is traversed.

To support the rejection, the Office bears the burden of establishing a prima facie case of obviousness. To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. M.P.E.P. § 2143.

The prior art fails to establish a prima facie case of obviousness, because taking the whole state of the art into consideration, there would have been no motivation in 1999 for a person of ordinary skill in the art to have considered Lechner and Blache individually or in combination in designing a treatment for Parkinson's disease.

The Examiner has alleged that it would be obvious to use the compounds of Blache in a treatment for Parkinson's disease, because Blache teaches compounds having putative platelet aggregation inhibiting properties and Lechner teaches that platelet aggregation occurs in Parkinsonism patients.

Applicants previously presented evidence that at the time the application was filed, platelet aggregation was not considered a cause of Parkinson's disease. The Examiner has responded that even though platelet aggregation was not considered an underlying cause of

Parkinson's disease does not mean that a skilled artisan would not provide an agent to a PD patient to treat a known symptom. OFFICE ACTION DATED APRIL 10, 2007, at 5.

Applicants respectfully point out that in addition to showing that platelet aggregation was not, and is not, considered an underlying cause of Parkinson's disease, the previously submitted evidence also showed that the prevailing concerns directing development of treatments for Parkinson's disease did not include treatment of any symptom related to platelet aggregation.

Submitted with this reply, Applicants present additional evidence that one of skill in the art would not have looked to Lechner and Blache in designing a treatment for Parkinson's disease. In the attached declaration pursuant to 37 C.F.R. § 1.132, Dr. Laura Bossi testifies that a person of ordinary skill in the art from 1999 to the present would not have considered that Parkinson's disease is caused by vascular lesions, that there is significant vascular involvement in Parkinson's disease, or that an increased vascular risk profile is associated with Parkinson's disease. In particular, a person of ordinary skill in the art would not have considered platelet aggregation to be a factor in Parkinson's disease.

Dr. Bossi testifies that throughout the 1990's levodopa therapy remained the treatment of choice for Parkinson's disease and research and development efforts were directed towards neuroprotective agents and novel dopaminergic drugs. The prevailing view did not consider vascular effects or platelet aggregation as a factor to consider in developing a treatment for Parkinson's disorder. Therefore, a person of ordinary skill in the art would not have considered any putative effects on platelet aggregation or other vascular effects in choosing an agent for use in a therapeutic composition for the treatment of Parkinson's disease.

Dr. Bossi testifies that Lechner et al. reported results of a study on an atypical group of patients with a Parkinson's like disorder that appears to involve a vascular risk. The term

"Lechner-Ott-Syndrome" is not found in the general literature on Parkinson's disease. Indeed, the cited article seems to stand alone. A person of ordinary skill in the art would not have considered the report by Lechner et al. in choosing a drug for treatment of Parkinson's disease, because the report of Lechner et al. concerns such an atypical group of patients and the observations of Lechner et al. were never repeated. To choose a drug for the treatment of Parkinson's disease on the basis of the Lechner et al. report would have been contrary to the conventional wisdom in the field in 1999, and today, regarding the causes and consequences of Parkinson's disease.

Dr. Bossi's testimony is supported by the expert report of another eminent researcher and clinician in the field of Parkinson's disease. Professor Christopher G. Goetz, M.D., of the Rush Medical Center in Chicago Illinois. Dr. Bossi consulted with Dr. Goetz in considering the alleged basis of the rejection. Dr. Goetz prepared an expert report addressing several inquiries put to him. Dr. Bossi testifies that his report and the opinions expressed therein are entirely consistent with her own knowledge and experience. A copy of Dr. Goetz's report is attached to Dr. Bossi's declaration and is incorporated by reference therein in its entirety.

Dr. Goetz's analysis shows, and Dr. Bossi testified, that Parkinson's disease and vascular parkinsonism are two distinct neurological conditions, and Parkinson's disease is not felt to relate to primary vascular pathology. This has been the prevailing view of persons of ordinary skill in the field throughout the time frame from 1999 to the present.

Dr. Goetz's analysis shows, and Dr. Bossi testified, that in 1999 as in the present, a person of ordinary skill in the art would have recognized that the small body of evidence for vascular involvement in Parkinson's disease suggests only minor involvement and such involvement may be indirect. In the time frame from 1999 to the present, a person of

ordinary skill in the art would have considered that vascular involvement is not a significant part of Parkinson's disease.

Dr. Goetz's analysis shows, and Dr. Bossi testified, that the evidence does not suggest that Parkinson's disease relates to a higher vascular risk profile. Indeed, the opposite may be the case. Therefore, a person of ordinary skill in the art in the time frame from 1999 to the present would not have considered vascular risk profile factors as relating to Parkinson's disease or that a diagnosis of Parkinson's disease implied an increased vascular risk.

Dr. Goetz's analysis shows, and Dr. Bossi testified, that there has been no conclusive evidence that platelet aggregation is a factor in Parkinson's disease. Moreover, because of the atypical nature of the patients in the group reported by Lechner, and the apparent lack of any other reference to a Lechner-Ott syndrome in the literature of the field, a person of ordinary skill in the art from 1999 to the present would not have looked to the Lechner report for guidance in developing a treatment for Parkinson's disease.

A declaration or affidavit is, itself, evidence that must be considered. M.P.E.P. § 2164.05. When an applicant puts forth rebuttal evidence, the Office must consider it. *In re Sullivan*, 84 USPQ2d 1034, 1040 (Fed. Cir. 2007). Rebuttal evidence is "merely a showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785 (Fed. Cir. 1984). When a patent applicant puts forth rebuttal evidence, the Office must consider that evidence. *See In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684 (Fed. Cir. 1995).

The evidence taken as a whole is overwhelming that platelet aggregation simply would not have been considered a factor in Parkinson's disease as either a cause or effect. According to the knowledge and conventional wisdom in the art, a person of ordinary skill simply would not have considered Blache and/or Lechner in designing a method of treating

Parkinson's disease. Accordingly withdrawal of the rejection over Blache and Lechner is respectfully requested.

Claims 15 and 16

In view of the foregoing, claims 15 and 16, which specifically recite an embodiment wherein the method of the invention is directed to treating Parkinson's disease, are respectfully submitted to be allowable, notwithstanding any other present ground of rejection. An indication that claims 15 and 16 are allowable is respectfully requested.

Blache and Neu

Claims 9, 10 and 12 stand rejected under 35 U.S.C. § 103 as allegedly unpatentable over U.S. Patent Number 5,523,322 ("Blache") in view of Neu et al., *Acta Neurol. Scandinav.* 66:497-504, 1982 ("Neu"). The rejection is traversed.

Neu is alleged to teach that platelet aggregation occurs in Multiple Sclerosis (MS) patients. The Office has contended that this teaching would make it obvious to treat MS using the compounds taught by Blache. Applicants previously presented evidence that at the time the application was filed, platelet aggregation was not considered a cause of MS. The Examiner has responded that even though platelet aggregation was not considered an underlying cause of Parkinson's disease does not mean that a skilled artisan would not provide an agent to a MS patient to treat a known MS symptom. OFFICE ACTION DATED APRIL 10, 2007, at 4.

Applicants respectfully point out that Neu did not show spontaneous platelet aggregation in MS patients. As previously explained, the authors of Neu performed measurements of artificially induced aggregation on 30 MS patients. Their conclusion is that "*...MS patients showed a (significantly) increased ADP- and serotonin-induced platelet*

aggregation." This is not a measurement of platelet aggregation in a native biological system (spontaneous aggregation) but in an induced system (via ADP or serotonin).

Regarding spontaneous aggregation, the authors merely hypothesized that spontaneous aggregation could be demonstrated but they don't show it! Their conclusion is that "*Neither the results of our own investigations provide a conclusive answer to the question of whether the platelet alterations in MS patients are epiphenomena of multiple sclerosis, or whether they are independent, pathogenetically relevant phenomena*" Neu at 503, §(1).

Thus, Neu cannot be held to have demonstrated even that platelet aggregation is a symptom of MS. Consequently, the alleged basis for maintaining the rejection is simply not supported by the cited reference.

But, furthermore, in addition to showing that platelet aggregation was not, and is not, considered an underlying cause of MS, the previously submitted evidence also showed that the prevailing concerns directing development of treatments for Parkinson's disease did not include treatment of any symptom related to platelet aggregation. Applicants respectfully point out that the previously submitted evidence effectively refutes the alleged reason for maintaining the rejection.

The review by McKhann in 1982 presented a representative overview of the state of the art in MS at the time Neu was published. McKhann, Ann. Rev. Neurosci., 5:219-39, 1982 (attached to the Reply filed November 6, 2006 as Exhibit F)("*The pathological analysis indicates a selective disease process with loss of myelin and oligodendroglia ... there remains the possibility that there is more generalized involvement of white matter or blood vessels.*")

But, Neu and McKhann were published in 1982 and as of 1999, there was no confirmation of Neu's hypothesis in the field. Thus, it is clear that in the years before 1999 Neu had no appreciable impact on persons of ordinary skill in the art notwithstanding the "possibility" of blood vessel involvement cited by McKhann. In 1993, Blache would have had the benefit of Neu's 1982 publication of their hypothesis. The fact that Blache et al. does not even mention MS shows that the teachings of Neu would have been given no consideration by persons of ordinary skill in the art in possession of a compound capable of inhibiting platelet aggregation.

Indeed, in 1996, well after the publication of Neu and Blache, state of the art treatments of symptoms of MS did not include anti-platelet aggregation medications. Andersson et al. described the state of the art in Multiple Sclerosis Treatment, *West J Med*, 1996 (attached as Exhibit H to the Reply filed November 6, 2006). Fourteen years after Neu was published, patients were treated for symptoms of MS with: glucocorticosteroids and corticotrophin during acute exacerbations, bacoflen and physic exercises for spasticity, anticholinergic agents for bladder symptoms, dietary adjustments for bowel symptoms, amantadine hydrochloride, pemoline or fluoxetine hydrochloride for fatigue, antidepressant for depression (eg. amitriptyline, fluoxetine), tricyclic antidepressant (eg. amitriptyline) for pain syndromes, clonazepam for tremor and ataxia. No anti-platelet aggregation medication is indicated, because 14 years after Neu, the conventional wisdom did not consider platelet aggregation to be significant symptom for treatment.

In 1999, with a better knowledge of the development of the pathology of MS, interferon beta and anti-inflammatory drugs were included among drugs believed to act on the course of the disease. See, Larner et al., British Medical Journal, 319-362-6, 1999 at 363 1st column (attached as Exhibit I to the Reply filed November 6, 2006); and, Parish et al.,

Immunology and Cell Biology, 76:104, 1998 abstract only (attached as Exhibit J to the Reply filed November 6, 2006). In 1999, no drugs approved to treat MS were directed to regulation of platelet aggregation or intended to act on any vascular problem. Rudick, Arch. Neurol., 56:1079-84, 1999 (attached as Exhibit K to the Reply filed November 6, 2006) in its article entitled "*Disease-Modifying drugs for relapsing-remitting MS and future directions for MS therapeutics*" gives an overview of the state of the art with regards to disease modifying therapies for MS back in 1999. Table 1 (page 1080) lists the drugs approved by the FDA.

Thus, it is clear that the evidence taken as a whole simply does not support the alleged basis for maintaining the rejection. Consequently, withdrawal of the rejection over Blache and Neu is appropriate and respectfully requested.

Furthermore, there being no reason for rejecting the present claims that is supported by the evidence taken as a whole, an indication that all the claims are allowable is respectfully requested.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such questions so that prosecution of this application may be expedited.

The Director is hereby authorized to charge any appropriate fees that may be required by this paper, and to credit any overpayment, to Deposit Account No. 02-4800.

Respectfully submitted,

BUCHANAN INGERSOLL & ROONEY PC

Date: October 10, 2007

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